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INSIDE

Changes Due to Radiation Fibrosis Can Be Reversible with a Simple Oral Regimen

ABSTRACT & COMMENTARY

Synopsis: Investigators in Paris performed a follow-up phase III randomized trial to confirm the efficacy and synergism of pentoxifylline and alpha-tocopherol as an antifibrotic treatment in women who had received previous breast radiotherapy. Results of their earlier phase II trial indicated that the 2 drugs act via complementary mechanisms to break the self-perpetuating cycle of tissue damage, with continued improvement over time. The earlier trial results were confirmed in the randomized trial, and the investigators have suggested larger trials to establish their regimen as the standard approach for treatment of this "orphan disease."

Source: Delanian S, et al. *J Clin Oncol.* 2003;21:2545-2550.

Radiation-induced fibrosis (rif) is most often considered to be an irreversible process involving nonspecific changes in the connective tissue and has been associated with extracellular matrix deposition and hyperactive fibroblasts. The process generally stabilizes or progresses, with sporadic acute inflammatory periods. It is felt to involve a dynamic process combining atrophy/contraction and connective tissue hypertrophy/fibrosis. Although there is no effective treatment for this condition, it has been reported in the literature that the use of pentoxifylline[1] and superoxide dismutase[2] can promote healing of radiation-induced tissue damage. On that basis, Delanian and colleagues hypothesized that alpha-tocopherol might offer an antioxidant benefit similar to that shown for superoxide dismutase since the latter is not readily available. Since their unpublished results with either agent alone showed little effect on RIF, they conducted a Phase II trial to explore possible synergies between the 2 agents and found that 66% RIF regression occurred at 1 year.[3] Given these results, Delanian et al embarked on a phase III double-blind randomized trial using a 2×2 factorial design. The main end point was relative regression of the fibrotic surface area at 6 months.

Between 1998 and 2000, 31 women with postradiotherapy breast fibrosis were enrolled in a 4-arm trial. Seven were excluded because

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they did not have measurable fibrosis or their fibrosis was shorter than 6 months' duration. The etiology of the fibrosis was attributed to either prior breast brachytherapy or the junction of breast and nodal external beam fields. The mean time to development of RIF was 7 ± 4 years. The mean initial diameter of RIF was 6.5 cm, depth was 2.1 centimeters, and surface area was 41 square centimeters. Fifteen patients had received "combined chemotherapy." The 24 study patients were randomized to Group A: pentoxifylline 800 mg q.d. and Vitamin E 1000 IU q.d.; Group B: pentoxifylline + Vitamin E placebo; Group C: pentoxifylline placebo + Vitamin E; and Group D: double placebo. The study drugs were given for 6 months. Patients were then evaluated for RIF surface area and volume changes using palpation, ultrasound, and the Subjective Objective Medical management and Analytic evaluation of injury (SOMA) scale. The latter grades scaliness, pruritus, pain, local edema, alterations in pigmentation, ulceration, necrosis, fibrotic scarring, atrophy, and tissue contraction.

There were 22 evaluable patients. One patient withdrew at the outset and another withdrew during the trial because of intercurrent psoriasis. Both drugs were well tolerated. Clinical regression of RIF was defined as centripetal reduction of the edges of the fibrotic block without contraction. The combined pentoxifylline/Vitamin E patients demonstrated significantly better regression of RIF measured by surface area at 6 months than did the double placebo group (60% vs 43%; P = .038) and a trend toward better RIF volume regression (73% vs 51%; P = .054).

Delanian et al concluded that, despite the small sample size, their randomized trial confirmed the results of their earlier phase II trial, as well as previous animal studies. They felt that 6 months was almost too short to observe a significant improvement but that a reversal of the fibroatrophic process was achieved. The precise mechanism of chronic radiotherapy damage reduction is unknown, but pentoxifylline is a methyl xanthine derivative that seems to effect dermal fibroblast proliferation and extracellular matrix production, while vitamin E scavenges reactive oxygen species. The TGF beta-1 pathway has been implicated in the overall process. Given that long-term follow-up of their phase II patients showed progressive improvement that peaked at 18-36 months, Delanian et al speculated that the current study patients may have further RIF regression. Larger trials are needed to confirm their findings.

COMMENT BY EDWARD J. KAPLAN, MD

In my opinion, Delanian et al are to be commended for their innovative approach and tenacity in their mission to evaluate an antifibrotic regimen in patients suffering from postradiation soft-tissue toxicity. Their work has spanned more than 10 years and consisted of animal studies right on through to a randomized trial. Delanian et al appear to be mostly alone in the quest for treatment of a fairly common but neglected problem. As Moulder pointed out in a recent article about pharmacological intervention for radiation injuries, the behavior of parenchymal and vascular cells can be modulated such that deleterious responses to radiation are not necessarily inevitable. "Unfortunately, assessment of the utility of these agents for clinical use has been minimal, and there are no established mechanisms for any of the experimental or clinical successes."[4] Aside from a couple of case reports, there is almost nothing published about the pentoxifylline/vitamin E regimen by authors other than Delanian et al. Gottlober from Germany presented a 58-year-old woman who was treated with pentoxifylline 1200 mg + vitamin E 400 mg q.d. following surgery in an area of postradiation fibrosis. Skin thickness was measured via ultrasound, and improvement was noted beginning at 4 months. Continued improve-

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ment was seen beyond 6 months.[5] Another German group reported on a breast cancer patient treated with pentoxifylline 1200 mg + Vitamin E 400 mg q.d. for ulcerating RIF. The ulcers were nearly healed by 18 months.[6] Neither case report found any side effects from treatment.

I was somewhat dismayed at the low patient numbers in the Delanian trial, but I am confident that the regimen has activity that can reverse postradiation fibrotic changes. I have used the regimen on my own patients since the phase II data were published, and I have seen excellent outcomes with it. Hot, swollen, or firm tissue can regain its natural texture and contour with continued use of these agents. I am hopeful that this line of study will be explored further by a cooperative group or large institution with the resources to enroll sufficient numbers of patients so that compelling data may be generated. ■

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Choosing the Right Chemotherapy for Elderly NSCL Cancer Patients

ABSTRACT & COMMENTARY

Synopsis: The current report examines the importance of patient age with regard to toxicity and response rates when treated with carboplatin and paclitaxel for advanced lung cancer. Similar toxicity profiles were observed in those younger or older than 70 years of age, and response rates were also similar.

Source: Hensing TA, et al. *Cancer.* 2003;98: 779-788.

There remains controversy about the optimal treatment for patients with lung cancer who are older than 70 years. In a previously reported[1] phase-III trial with no age restriction, the duration of therapy with carboplatin and paclitaxel was compared for patients with stage IIIB or IV non-small-cell lung cancer. The findings indicated that there was no difference in survival or in quality of life when treatment was extended beyond 4 cycles. The current report reexamines these data set in the context of patient age. Of the 230 patients who were subjects of the earlier report, 67 were 70 years or older (29%). These patients were compared with those younger than 70 receiving the same treatment regimens. The chemotherapy involved the use of carboplatin at an area under the curve (AUC) of 6 and paclitaxel at a dose of 200 mg/m^2 every 21 days. Individuals received either a scheduled 4 cycles of this combination or additional cycles until there was evidence for disease progression. As it turns out, the median number of cycles delivered for both age groups was 4 cycles (range, 0-19 cycles). There were no statistically significant differences in any of the most common toxicities observed in patients younger than age 70 years compared with patients age 70 years and older. This included neutropenia (38% vs 35%), neuropathy (13% vs 16%), myalgia/arthralgia (15% vs 9%), malaise (8% vs 15%), anemia (9% vs 4%), thrombocytopenia (7% vs 9%), anorexia (8% vs 4%), and nausea/emesis (14% vs 15%).

Hensing and colleagues concluded that their analysis demonstrated that carboplatin/paclitaxel exhibited similar toxicity profiles in patients age 70 years and older compared with patients younger than age 70 years. The survival rates were not different between the 2 age groups, and there was no difference in progression or quality-of-life outcomes. Thus, they concluded that in fit, elderly patients carboplatin/paclitaxel combined therapy represented a reasonable standard regimen, inasmuch as no excessive toxicity was observed and efficacy was comparable to younger patients.

■ COMMENT BY WILLIAM B. ERSHLER, MD

This reports highlights what many practicing oncologists have understood for some time, that older patients who are referred to and eligible for clinical trials using combination chemotherapy regimens are likely to fare generally as well as younger patients. It is encouraging to see some additional solid data that reflect this clinical impression.

The problem, however, comes in the determination of the appropriate patients for combined agent therapy. What remains is a bias with regard to entering elderly patients onto study. Despite concerted efforts at recruitment, the "typical" older patients are disproportionately under-represented in such clinical trials.

For example, in the current study only 29% of the patients enrolled were older than age 70, whereas registry data indicate that the median age for incipient lung cancer is approximately 70 years. Thus, although half the patients in the general community with lung cancer are 70 years or older, only approximately a quarter of the current trial fell into this age group. Of course, it may be that older patients prefer not to be on trial because of the logistical problems involved in frequent clinic visits, aggressive testing, etc. Probably more likely, however, is that older patients, by virtue of age-associated comorbidities, are less likely to be eligible for study. Thus, despite the appeal of the current findings, the implications for the "typical" geriatric lung cancer patient remain to be clarified. Certainly, the current report would suggest that physiologically fit older patients should be treated with standard regimens in a manner similar to younger patients.

The issue of what to do with the "typical" geriatric patient who does have comorbidities and a performance score below a Karnofsky of 70 remains to be determined. There have been recent reports, particularly from Italy, indicating the use of single-agent treatment, either vinorelbine or gemcitabine,[2,3] suggesting that observed tumor regression and maintained quality of life were better in treated individuals than that compared to those receiving just supportive care. Which single-agent use remains unclear. When vinorelbine was compared directly with gemcitabine for example, responses rates were comparable.[3]

The optimal treatment for elderly patients with advanced NSCL cancer remains uncertain. The data presented would suggest that the commonly used standard approach of carboplatin and paclitaxel is well tolerated in elderly patients, and certainly this approach is reasonable for those who are fit and without significant comorbidity. Further research is clearly called for with regard to defining the optimal treatment for the typical geriatric lung cancer patient. Use of a somewhat more detailed pretreatment assessment tool and the evaluation of the importance of various comorbidites would seem likely targets for investigation, in the context of either single-agent or combination chemotherapies. ■

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Breast Cancer and HRT: The Million Woman Study

ABSTRACT & COMMENTARY

Synopsis: The Million Women Study, a cohort study of a quarter of all British women aged 50-64, was undertaken to investigate the relationship between the various patterns of HRT use and breast cancer incidence and mortality. During a 5-year period (1996-2001), 1,084,110 women were followed for breast cancer incidence and death. Current users of estrogen or estrogen-progestin combinations were shown to have a significantly higher risk of developing and dying from breast cancer. The findings confirm and extend those published last year by the Women's Health Initiative.[1]

Source: Million Women Study Collaborators. Breast cancer and hormone replacement therapy in the Million Women Study. *Lancet.* 2003;362:419-427.

The million woman study was undertaken between the years 1996 and 2001, during which time 1,084,110 UK women provided information about their use of hormone replacement therapy (HRT), as well as other personal details, and were then followed for cancer incidence and death. The participants in the study represent approximately 25% of the UK women in this age group. Approximately half of the women reported current or past use of HRT. During the 5 years of study there were 9364 incident invasive breast cancers and 637 breast cancer deaths after an average of 2.6 and 4.1 years of follow-up, respectively. Current-users of HRT at recruitment were more likely than never-users to develop breast cancer (adjusted relative risk, 1.66 [95% CI, 1.58-1.75; $P < .0001$) and die from it (1.22 [1.00-1.48]; $P = .05$). However, past-users of HRT were not at an increased risk of incident or fatal disease (1.01 [0.94-1.09] and 1.05 [0.82-1.34], respectively). Incidence was significantly increased for current-users both of preparations containing estrogen only (1.30 [1.21-1.40]; $P < .0001$) or estrogen-progestin (2.0 [1.88-2.12]; $P < .0001$), but the magnitude of the associated risk was substantially and significantly greater for estrogen-progestin than for other types of HRT ($P < .0001$). When looked at separately, relative risks were significantly increased for users of oral, transdermal, and implanted estrogen formulations ($P < .0001$). In current-users of each type of HRT the risk of breast cancer increased with increasing total duration of use. Ten years use of HRT was estimated to result in 5 (95% CI,

3-7) additional cancers per 1000 users of estrogen-only preparations, and 19 (15-23) additional cancers per 1000 users of estrogen-progestin combinations.

■ COMMENT BY WILLIAM B. ERSHLER, MD

This large epidemiologic study confirms the association of HRT and breast cancer. Furthermore it demonstrates an increased risk for all types of HRT, including estrogen alone or transdermal formulations. The estrogen-progestin combinations seem to be the most dangerous with regard to the development of breast cancer. The duration of HRT use appears to be important, and those current users having been treated for a decade or more were at particularly high risk. To put these findings in perspective, among women from developed countries who never used HRT the incidence of invasive breast cancer is estimated to be typically 32 in every 1000 between the ages of 50 and 65.[2] The cumulative incidence of breast cancer per 1000 associated with different patterns of use of HRT, calculated by applying the relative risk estimates determined in this study to the estimated incidence rates in never-users of HRT, showed that by 5 years use of HRT, beginning at the age of 50, it would be estimated to result in 1.5 additional breast cancers by the age of 65 among 1000 users of estrogen-only preparations, and 6 (CI, 5-7) additional cancers per 1000 users of estrogen-progestin combinations. By 10 years the use is estimated to result in 5 (CI, 3-7) additional cancers in 1000 users of estrogen only, and 19 (CI, 18-20) additional cancers in 1000 users of combined HRT. Looked at another way, use of HRT by UK women, age 50-64 years, in the most recent decade is estimated to have resulted in an extra 20,000 incident breast cancers.

Thus, the cumulated data from this and other well-constructed studies[1, 3-5] indicate an irrefutable association between breast cancer and HRT use. The estimated increased numbers are of great consequence, and physicians need to be aware and to discuss these increased risks if patients are to undertake such treatment approach. As described in the accompanying editorial,[6] "The new evidence of breast cancer mortality dictates an explicit position for general practitioners—HRT should be discouraged and, for women presenting with new postmenopausal related health problems, general practitioners should seek alternative solutions." With the current data, it is difficult to find fault with that recommendation. ■

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Weekly Cisplatin and Gemcitabine with Concurrent Radiotherapy in Locally Advanced Cervical Carcinoma

ABSTRACT & COMMENTARY

Synopsis: The association of cisplatin and gemcitabine with concurrent radiotherapy is active and well-tolerated in untreated LACC.

Source: Zarba JJ, et al. *Ann Oncol*. 2003;14: 1285-1290.

Cervical cancer is the most frequent gynecologic cancer in the world and the most frequent cancer in women in many underdeveloped and developing countries, where almost half of the patients are diagnosed with locally advanced disease. Older women, particularly minorities, have the highest incidence of mortality (http://www.seer.cancer.gov/). The current standard of care is the concurrent administration of chemotherapy and radiotherapy.[1] It has been shown to improve the control of pelvic disease and significantly increase overall survival rates in numerous randomized trials.[2-6] The most widely used chemotherapeutic agent is cisplatin, but not a single drug or schedule is accepted as standard. In randomized trials, weekly cisplatin 40 mg/m^2 with concurrent radiotherapy has an acceptable therapeutic ratio. Despite these improvements, there is a need for further optimization of care. Gemcitabine has shown some single-agent activity in metastatic or recurrent cervical cancer and has shown radiosensitizing properties in preclinical trials. Patients have been treated with concurrent radiotherapy and gemcitabine at a dose of 150-300 mg/m^2 with acceptable toxicity and favorable outcome. The current study was designed to determine whether the addition of gemcitabine to cisplatin 40 mg/m^2 and concurrent radiotherapy is safe and feasible.

■ COMMENT BY STUART M. LICHTMAN, MD, FACP

This trial involved women with untreated invasive squamous cell carcinoma of the cervix with International Federation of Gynecology and Obstetrics (FIGO) stages IIB, III or IVA (involvement of the bladder or rectal mucosa). Patients with disease outside the pelvis and para-aortic lymph node metastases were ineligible. The performance status was 0-2. Radiotherapy was administered to the whole pelvic region in 28 fractions for a total of 50.4 Gy followed 1 or 2 weeks later by intracavitary brachytherapy. The chemotherapy consisted of cisplatin that was administered weekly at 40 mg/m^2. Gemcitabine was given as a 30-min infusion started at 75 mg/m^2 and escalated with a 25-mg/m^2 increment in successive cohorts of 3 patients.

At a dose of 125 mg/m^2 grade 3 toxicity was observed, while at 150-mg/m^2 grade 4 toxicity occurred (diarrhea, skin). Therefore, the 125 mg/m^2 dose was considered the maximal tolerated dose (MTD). The study was expanded, and 26 patients were treated at the MTD. In this phase II study, 3 grade 3 toxicities (diarrhea, mucositis, nausea, and vomiting) occurred in 11.5% of patients. Grade 4 toxicities were less than 5%. The overall objective response rate was 97.3% (PR 8.3%). At a median follow-up of 26 months, median disease free survival (DFS) and overall survival (OS) were not reached. The 3-year DFS rate is 67%, and the OS rate is 72%.

Advanced cervical cancer is common in developing countries often due to lack of screening and early detection programs. In the United States older women have the highest incidence of mortality from this disorder. Therefore, locoregional control is important to improve survival. A major advance in therapy was the result of 5 randomized phase III trials, which have shown an OS advantage for cisplatin-based therapy given concurrently with radiation therapy. While study design varied, they all demonstrated significant survival benefit for combined modality therapy, decreasing the risk of death by 30-50%. Despite the superiority of the combined approach, the local recurrence rate was still between 19% and 24%. Gemcitabine is a known radiosensitizer and has been studied in pancreatic cancer, non-small-cell-lung cancer, cervical cancer, and head and neck cancer. Concomitant radiation and the gemcitabine/cisplatin combination has been evaluated in pancreatic and non-small cell lung cancer. These reported study results are in the same range that has been reported in the randomized trials. There is a clear need for newer therapies in this lethal disorder. This trial is a first step in this regard, particularly with its low reported toxicity. The study limitations are its small size and the median age of 48 years. While this is probably representative of many patients in less-developed countries, it is approximately 20 years less than many of the women in the United States who are treated for locally advanced disease. Trials in which cisplatin is combined with another radiation sensitizer (ie, gemcitabine, paclitaxel) need to be studied in an older and less fit population to truly determine whether it can be used to treat a large number of patients. As approximately 50% of recurrences occur outside the radiation field, better systemic therapies also need evaluation. ■

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Hepatitis C and Non-Hodgkin's Lymphoma: An Association Clarified

ABSTRACT & COMMENTARY

Synopsis: In this multicenter Italian study the prevalence of hepatitis C infection (HCV) was 17.5% among 400 newly diagnosed non-Hodgkin's lymphoma patients compared to 5.6% among controls, confirming an association between these 2 disorders. The suggestion is made that such patients should be studied to both determine the role of the HCV in the pathogenesis of lymphoma and to determine the effects of antiviral therapy on lymphoma progression.

Source: Mele A, et al. *Blood*. 2003;102:996-999.

Hepatitis c virus (hcv) remains a major cause of chronic liver disease throughout the world and an association with non-Hodgkin's lymphoma (NHL) has been described.[1,2] It has been proposed that hepatitis C may be involved in the pathogenesis of the lymphoma in those patients who have been shown to have both illnesses. If such were the case, then one might expect to see evidence for HVC greater in patients with lymphoma than in the general population. Indeed, a positive

association has been found in studies conducted in countries where the prevalence of HCV infection is relatively high (eg, Italy, United States) but not in other countries).

The objective of the current study performed throughout Italy was to evaluate the potential association between B-cell NHL and HCV. A multicenter, case-controlled study was undertaken including only patients with newly diagnosed B-cell NHL. From January 1998 through February, 2001 all new cases of NHL were catalogued. Control patients were individuals from other departments within the same hospitals. Both groups were interviewed, and the prevalence of HCV infection was calculated. Adjusted odds ratio (OR) and HCV-attributable risk (AR) were estimated.

HCV prevalence was 17.5% among the 400 lymphoma patients and 5.6% among the 396 controls. The adjusted odds ratio of NHL (patients vs controls), adjusted by age, sex, level of education, and place of birth was 3.1 (95% confidence interval, 1.8-5.2), and OR indicative of positive association was found for indolent and aggressive B-cell NHL. The estimated AR was 4.6%.

This study confirms an association between HCV and B-cell NHL. In Italy, where the incidence of HCV is considered high, comparable to that in the United States, 1 of 20 B-cell non-Hodgkin lymphoma patients may have coexisting hepatitis C infection. The authors speculate that this may turn out to be useful information inasmuch as antiviral therapy may be important in the management of both the HCV infection and lymphoma in these patients.

COMMENT BY WILLIAM B. ERSHLER, MD

The current cooperative investigation has the merits of evaluating only new cases of NHL over a relatively short period of time throughout a country (Italy) in which HCV is known to be fairly prevalent. The findings demonstrate, without a doubt, an association of HCV and lymphoma. In fact, patients with newly diagnosed NHLs were found to be 3.1 times more likely to be infected with HCV than controls. Also of note, the increased risk of HCV infection was observed for both aggressive and nonaggressive lymphoma histologies. Furthermore, there did not seem to be a difference in the hepatitis C genotypes (1b, 2a/2c) when compared to the prevalence of these genotypes in the general Italian community. This would suggest that the association of lymphoma with HCV infection is not genotype specific.

Mele et al were very careful to match, as best possible, the controls (hospitalized patients without lymphoma) with patients. When adjustments were made for age, sex, level of education, place of birth, and other possible confounders, the observed risk of HCV infection remained significantly greater for NHL patients than controls.

This finding warrants consideration and additional investigation. Recently it has been reported that patients with HCV and splenic lymphoma had regression of disease when treated with interferon and Ribavirin, the standard approach for HCV infection.[3] Accordingly, as has been the case in other virally associated lymphomas, such as those that occur in the transplant setting, therapeutic trials of antivirals may prove useful in the management of the lymphoproliferative disorder. Clearly, this approach needs to be subjected to rigorous clinical investigation. ■

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CME Questions

8. In the Delanian trial, pentoxifylline and tocopherol were used in an effort to reverse postradiation fibrosis that:

a. developed during the course of breast radiotherapy.
b. occurred within the 6 months following completion of radiotherapy.
c. was measurable and occurred beyond 6 months from completion of treatment.
d. did not respond to any other intervention.

9. The regimen used by Delanian et al was:

a. pentoxifylline 1200 mg + vitamin E 400 IU q.d.
b. pentoxifylline 1200 mg + vitamin E 400 IU q.d.
c. pentoxifylline 800 mg + vitamin E 1200 IU q.d.
d. pentoxifylline 800 mg + vitamin E 1000 IU q.d.

10. Best results from the pentoxifylline/Vitamin E treatment for postradiation fibrosis plateaued:

a. 0-6 months.
b. 7-12 months.
c. 13-18 months.
d. Beyond 18 months.

11. Regarding treatment of elderly patients with advanced lung cancer, which of the following statements can be supported by the data from Hensing et al?

a. Treatment of the "fit" elderly patient with paclitaxel and carboplatin results in a comparable level of toxicity and efficacy.
b. Treatment of the "fit" elderly patient with paclitaxel and carboplatin results in a greater toxicity but comparable efficacy.
c. Treatment of the "typical" elderly patient with paclitaxel and carboplatin results in a comparable level of toxicity and efficacy.
d. Treatment of the "typical" elderly patient with paclitaxel and carboplatin results in a greater toxicity but comparable efficacy.

12. In the case control series from Italy, which of the following conclusions about hepatitis C and non-Hodgkin's lymphoma is supported by the data presented?

a. Approximately 4% of all newly diagnosed lymphomas are in individuals with coexisting hepatitis C.
b. Approximately 20% of all newly diagnosed lymphomas are in individuals with coexisting hepatitis C.
c. Approximately 4% of all HCV-infected patients have lymphoma.
d. Approximately 20% of all HCV-infected patients have lymphoma.

13. The risk for developing breast cancer is increased for women (aged 50-65 years) who are currently using which of the following HRT preparations?

a. Oral estrogen
b. Oral estrogen-progestin combinations
c. Transdermal estrogen
d. Implanted estrogen
e. All of the above

Answers: 8:(c), 9:(d), 10:(d), 11:(a), 12:(b), 13:(e)

In Future Issues:

Growth Factors and the Treatment of Acute Leukemia